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10/765,727	01/23/2004	Mark William Bodmer	674525-2010	2653

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,727	BODMER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10,12,14,21-28 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *8,10,12,14 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-28,30 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *8,10,12,14,21-28, 30-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004 and 28 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 08 December 2008 has been entered in full. Claims 21, 22, 23, 25-28, 30, 33-38 are amended. Claims 1-7, 9, 11, 13, 15-20, 29, are cancelled.

Claims 8, 10, 12, 14, and 31-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07 August 2007.

Claims 21-28, 30, 33-38 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claims 33-34, 36, and 37 at pages 3-4 of the previous Office Action (09 July 2008) is *withdrawn* in view of the amended claims (08 December 2008).

2. The rejection of claims 21-24, 26-27 under 35 U.S.C. § 102(b) as being anticipated by Lamb et al. ("Lamb2"; WO 00/36089) is *withdrawn* in view of the amended claims and Applicant's persuasive arguments (08 December 2008).

3. The rejections of claim 29 under 35 U.S.C. § 112, first paragraph (enablement) and 35 U.S.C. § 102(b) as being anticipated by Lamb1 are *withdrawn* in view of the cancelled claim (08 December 2008).

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-28, 30, 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claims 21-30 and 33-38 at pages 4-9 of the previous Office Action (09 July 2008) and at pages 6-10 of the Office Action of 16 October 2007.

The claims are directed to methods for reducing a TH2 and TH1 immune response in a subject in need thereof comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for treating inflammation, an inflammatory condition or an autoimmune condition comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for modifying cytokine expression in cells of the immune system of a patient in need thereof comprising administering a modulator of Notch signaling to said patient to modify cytokine expression of said patient's cells *in vivo,* wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain. The claims recite a method for modifying cytokine expression in cells of the

immune system of a patient in need thereof comprising (i) administering a modulator of Notch signaling to the cells of said subject *ex vivo,* wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain ; and (ii) administering said cells in which cytokine expression is modified to the subject. Finally, the claims recite a method for treating a disease associated with excessive TNFα production, excessive IL-5 production or excessive IL-13 production, comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine expression is modified, to the subject. Claims 33-38 are directed to methods of administering a modulator of Notch signaling to a subject in need thereof.

Applicant's arguments (08 December 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page of the Response of 08 December 2008, Applicant argues that the instant claims now clarify the modulator of the Notch signaling pathway of the claimed invention, thereby modifying the breadth of the claims. Applicant asserts that in light of the instant claim scope, the skilled artisan can apply the modulators and perform the claimed invention without undue experimentation. Applicant asserts that the specification provides substantial guidance for the instant modulators of the claimed invention. Applicant indicates that the specification describes the Notch DSL domain and the Notch ligand EGF-like domain (pages 39-41). Applicant contends that the working examples, such as Examples 2, 4, 6, 10, and 14, demonstrate a

modulator of Notch signaling pathway comprising or encoding a Notch ligand DSL domain and at least one EGF-like domain.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches utilizing a fusion protein comprising the extracellular domain of mouse Delta1 (a Notch ligand) fused to the Fc domain of IgG4 in several *in vitro* examples (Examples 2, 4-6, 10, 14; termed, Fc-delta). As discussed in the previous Office Action, Example 5 of the specification teaches culturing various lymphocytes (such as TH1 and TH2 cells) in the presence of and absence of Fc-delta and measuring cytokine production (Figure 9, pages 95-96, 97-98). The Examiner acknowledges that the fusion protein, Fc-delta, alters the expression of IL-10, IL-13, IFNγ, and IL-2 in TH1 and TH2 cells *in vitro*. However, the claims of the instant application still broadly encompass methods of utilizing a modulator of Notch signaling wherein the modulator comprises a protein or polypeptide comprising a notch ligand DSL domain and at least 1 EGF-like domain. The specification does not disclose any methods or working examples indicating the functional activity of any modulator that comprises a notch ligand DSL domain and at least 1 EGF-like domain, other than Fc-delta. Relevant literature even teaches that distinct Notch ligands mediate differential effects of Notch signaling (Jaleco et al. J Exp Med 194(7): 991-1001, 2001; abstract). Jaleco et al. state that for example Notch ligands, Delta1 and Jagged1, "have differential effects in cell-fate decision processes in lymphopoiesis in vitro, strongly suggesting that the interplay of Notch receptors with distinct ligands may underlay diverse biological outcomes of Notch signaling pathways" (J Exp Med 194(7): 991-1002, 2001; page 992, bottom of column 1 through the top of column 2). Thus, undue experimentation would be required of the skilled artisan to generate a

modulator of the Notch signaling pathway that comprises a protein or polypeptide comprising any Notch ligand DSL domain in combination with any EGF-like domain, and then screen the modulator for activity. As discussed in the previous Office Action, according to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis".

The specification teaches at page 38 that the DSL domain may be derived from any suitable species, including for example, Drosophila, Xenopus, rat, mouse or human (lines 31-34). The specification discloses that a DSL domain may have at least 30%, 50%, 60%, 70%, 80%, 90%, or 95% amino acid sequence identity to the DSL domain of human Jagged1, Jagged2, Delta 1, Delta 3, or Delta 4 (page 38, lines 36-37; page 39, lines 1-22). At pages 36-37, the specification also teaches the amino acid residues comprising the DSL domains in the various Notch ligands. In a similar fashion, the specification teaches that the EGF-like domain may be derived from any suitable species, including for example, Drosophila, Xenopus, rat, mouse or human (lines page 40, lines 29-32). The specification discloses that an EGF-like domain may have at least 30%, 50%, 60%, 70%, 80%, 90%, or 95% amino acid sequence identity to the EGF-like domain of human Jagged1, Jagged2, Delta 1, Delta 3, or Delta 4 (page 40, lines 34-37; page 41, lines 1-19). The specification even indicates at pages 36-37 that human Jagged 1 and human Jagged2 have 16 EGF-like domains. The specification teaches that the present invention also encompasses the use of variants, derivatives, analogues, homologues, mimetics, and fragments

thereof (page 45, lines 25-27). Thus, the Examiner has broadly interpreted the claims as encompassing any modulator comprising a protein or polypeptide comprising any DSL and EGF-like domains, including an infinite number of domain variants and fragments. It is also noted that the claims do not limit the number of EGF-like domains that the modulator may contain. The specification does not teach a modulator comprising all possible DSL and EGF-like domains, including variants, fragments, or derivatives. The specification also does not teach functional or structural characteristics of the modulator comprising DSL and EGF-like domain variants, fragments, and derivatives, as encompassed by the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or

deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Thus, in view of the art, one skilled in the art would not be able to predict the function of the modulator of Notch signaling since it comprises a protein or polypeptide comprising a Notch DSL domain from any Notch ligand and at least one EGF-like domain from any protein.

Furthermore, the specification of the instant application even teaches that the EGF-like motif has been found in a variety of proteins, other than EGF and Notch and Notch-like ligands, including those involved in the blood clotting cascade, Drosophila genes, cell surface receptor proteins, thrombomodulin, urokinase (page 39, lines 25-33; page 40, lines 1-2). The art clearly teaches the existence of proteins with distinct functions having EGF-like domains wherein specific amino acids are required to provide specificity in protein functioning and wherein the deletion of even one amino acid from the EGF domain results in loss of function (see Van Zoelen et al., Vitam. Horm. 59: 99-131, 2000, Abstract;; Barbacci et al., J. Biol. Chem, 270: 9585-9589, 1995; Abstract, page 9587, column 1). McKnight et al. et al. also disclose that EGF

domains located within members of the EGF-TM7 family of seven-transmembrane-spanning cell-surface antigens contain a Ca^{2+}-binding consensus sequence (J Leukoc Biol 63: 271-280, 1998; page 277, column 1, 3rd full paragraph). Thus, one skilled in the art would not be able to predict the activity of a Notch modulator comprising at least one EGF domain (with any sequence) from a variety of different proteins. The specification does not provide any example of any EGF domain derived from a protein which is not a Notch ligand, wherein such EGF domain can function as Notch modulator together with the Notch DSL domain.

(ii) Applicant submits that determining the optimal dosage, duration, and administration route of the cells and modulators as claimed does not warrant undue experimentation. Applicant argues that one skilled in the art can determine the dosages and routes of experimentation as such work is routine, especially in light of the guidance provided in the specification (page 92, lines 1-32). Applicant states that the skilled artisan can apply the teachings of preparing the cells (pages 92-93) to perform the steps of the invention without undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. The instant specification teaches that cells of the immune system include, for example, antigen presenting cells (APCs), T cells, B cells, and dendritic cells (pages 52-53). However, the specification does not teach the administration of any immune system cell in which cytokine expression is modified or administration of any modulator of Notch signaling wherein the modulator comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain. A large quantity of experimentation would be required of the skilled artisan to determine the optimal dosage, duration, and route of administration of the cells and modulators

because the specification only outlines prophetic procedures for such. There is little guidance or methods disclosed in the specification to indicate that any cell of the immune system in which Notch is modulated, as well as any Notch modulator, reduces a TH1 response, reduces a TH2 response, treats diverse conditions or diseases, and modifies cytokine expression in cells of the immune system *in vivo*. The disclosed methods are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. McKenzie et al. (Sem Cell Dev Biol 14: 127-134, 2003) teach that "in mammalian systems, little is known about the extent to which different Notch ligands activate different receptors under physiological conditions, and whether there are distinct downstream signaling events triggered by different ligand/receptor combinations" (page 128, column 1, 1st paragraph). Also, the various diseases and conditions encompassed by the instant claims and disclosed in the specification have different pathophysiologies. Thus, one skilled in the art would not be able to predict that all possible modulators of Notch that comprise a protein or polypeptide comprising a DSL domain and at least one EGF-like domain or cells contacted with all possible Notch modulators would reduce a TH1 immune response; reduce a TH2 immune response; modify cytokine expression; treat inflammation, an inflammatory condition, or an autoimmune condition; or treat a disease associated with excessive TNFα production, excessive IL-5 production, or excessive IL-13 production, as required by the instant claims.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of Notch modulators comprising a protein or polypeptide comprising an infinite number of Notch ligand

DSL domains in combination with at least one EGF-like domain from any protein and screen the same for activity, as well as to administer all possible Notch modulators or cells of the immune system contacted with a Notch modulator to reduce a TH2 immune response, reduce a TH1 immune response, modify cytokine expression, treat an inflammatory or autoimmune condition, and treat a disease associated with excessive production of TNFα, IL-5, or IL-13; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and unpredictability of the *in vivo* effects of Notch modulators or cells of the immune system on the reduction of a TH2 immune response, reduction a TH1 immune response, modification of cytokine expression, treatment an inflammatory or autoimmune condition, and treatment a disease associated with excessive production of TNFα, IL-5, or IL-13, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

5. Claims 21-28, 30, 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods for reducing a TH2 and TH1 immune response in a subject in need thereof comprising (i) contacting a cell of the immune system with a modulator

of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for treating inflammation, an inflammatory condition or an autoimmune condition comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine expression is modified, to the subject. The claims recite a method for modifying cytokine expression in cells of the immune system of a patient in need thereof comprising administering a modulator of Notch signaling to said patient to modify cytokine expression of said patient's cells *in vivo,* wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain. The claims recite a method for modifying cytokine expression in cells of the immune system of a patient in need thereof comprising (i) administering a modulator of Notch signaling to the cells of said subject *ex vivo,* wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain ; and (ii) administering said cells in which cytokine expression is modified to the subject. Finally, the claims recite a method for treating a disease associated with excessive TNFα production, excessive IL-5 production or excessive IL-13 production, comprising (i) contacting a cell of the immune system with a modulator of Notch signaling to modify cytokine expression in the cell, wherein the modulator of Notch signaling comprises a protein or polypeptide comprising a DSL domain and at least one EGF-like domain; and (ii) administering said cell in which cytokine

expression is modified, to the subject. Claims 33-38 are directed to methods of administering a modulator of Notch signaling to a subject in need thereof.

The specification teaches at page 38 that the DSL domain may be derived from any suitable species, including for example, Drosophila, Xenopus, rat, mouse or human (lines 31-34). The specification discloses that a DSL domain may have at least 30%, 50%, 60%, 70%, 80%, 90%, or 95% amino acid sequence identity to the DSL domain of human Jagged1, Jagged2, Delta 1, Delta 3, or Delta 4 (page 38, lines 36-37; page 39, lines 1-22). At pages 36-37, the specification also teaches the amino acid residues comprising the DSL domains in the various Notch ligands. In a similar fashion, the specification teaches that the EGF-like domain may be derived from any suitable species, including for example, Drosophila, Xenopus, rat, mouse or human (lines page 40, lines 29-32). The specification discloses that an EGF-like domain may have at least 30%, 50%, 60%, 70%, 80%, 90%, or 95% amino acid sequence identity to the EGF-like domain of human Jagged1, Jagged2, Delta 1, Delta 3, or Delta 4 (page 40, lines 34-37; page 41, lines 1-19). The specification even indicates at pages 36-37 that human Jagged 1 and human Jagged2 have 16 EGF-like domains. The specification teaches that the present invention also encompasses the use of variants, derivatives, analogues, homologues, mimetics, and fragments thereof (page 45, lines 25-27). Thus, the Examiner has broadly interpreted the claims as encompassing any modulator comprising a protein or polypeptide comprising any DSL and EGF-like domains, including an infinite number of domain variants and fragments. It is also noted that the claims do not limit the number of EGF-like domains that the modulator may contain. The instant claims do not require that the modulator comprising a DSL domain and EGF-like domain possess any particular biological activity, nor any particular conserved

structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of modulators comprising an infinite number of possible DSL domains and EGF-like domains.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, complete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. However, in this case, the specification has not shown a relationship between the structure and function of the genus of Notch modulators comprising a DSL domain and at least one EGF-like domain. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of a protein fragment comprising the extracellular domain murine Delta1 fused to the Fc domain of IgG4 is not adequate written description of an entire genus of functionally equivalent Notch modulators comprising a DSL domain and at least one EGF-like domain.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at

page 1116).

Thus, the skilled artisan cannot envision the detailed chemical structure of Notch modulators comprising a protein or polypeptide comprising a Notch ligand DSL domain and at least one EGF-like domain, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 25, 28, 30, 33-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamb et al. ("Lamb1"; WO 98/20142; 14 May 1998). The basis for this rejection is set forth at pages 9-10 of the previous Office Action (09 July 2008).

Applicant's arguments (08 December 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

AT page 9 of the Response, Applicant argues that Lamb1 does not teach each and every limitation of the instant claims, which recites that the modulator of Notch signaling is modifying cytokine expression. Applicant asserts that Lamb1 indicates that treatment of conditions using Notch ligands is through other mechanisms, such as by inhibiting responses of antigen primed lymphocytes, preventing antigen priming of T lymphocytes, blocking or preventing T cells responses, or generating regulatory T cells.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Lamb1 teaches that the invention relates to the modification of Notch-protein expression or presentation of the cell membrane or signalling pathways (page 6, lines 5-6). Lamb1 continues to disclose that these have been shown to be involved in T cell mediated responses that participate in the induction of tolerance (page 6, lines 7-8). Lamb1 teach that the Notch-ligands (which activate Notch) used are preferably Delta or Serrate family members (page 10, lines 21-24). Lamb1 teach that Notch ligands have a diagnostic DSL domain comprising 20-22 amino acids at the amino terminus of the protein and between 3-8 EGF-like repeats on the extracellular surface (page 2, lines 12-14).

Lamb1 discloses that diseases or infectious states that are mediated by T cells and may be treated with use of the appropriate allergen or antigen and Notch-ligand include asthma, allergy,

graft rejection, autoimmunity, tumor induced aberrations to the T cell system, and infectious diseases (page 8, lines 17-25). As indicated in the previous Office Action, at the time the instant invention was made, it was well-known in the art that diseases and disorders, such as asthma, allergy, graft rejection, autoimmunity, tumor induced aberrations to the T cell system, and infectious disease, were associated with Th1/Th2 immune responses and excessive cytokine production by cells of the immune system (see for example, Spellberg et al. Clin Infect Disease 32: 76-102, 2001; Barnes, P.J., J Allergy Clin Immunol 108: S72-S76, 2001). For example, Dong et al. indicate that Th1 cells produce proinflammatory cytokines such as interferon-γ and lymphotoxin-α, while Th2 cells produce IL-4, IL-5, IL-9, IL-10, and IL-13 (Curr Opin Hematol 8:47-51, 2001; page 47, first full paragraph; cited in previous Office action of 09 July 2008).

Although Lamb1 does not specifically state "modifying cytokine expression", it is inherent that by modifying Notch signaling pathways and treating diseases or infectious states that are mediated by T cells, cytokine expression of cells of the immune system (such as T cells) would also be modified. One of ordinary skill in the art is also not required to recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)). The methods of Lamb1 modify cytokine expression in cells of the immune system, absent evidence to the contrary (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). Applicant has not provided any evidence to indicate that the method of Lamb1 would not modify cytokine expression in cells of the immune system. Thus, Lamb1 anticipates the claimed invention of the instant application.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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